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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/540,939

06/23/2005

Alberto Perbellini

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3804

7590 07/03/2007
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New York, NY 10017-5621

EXAMINER

KRISHNAN, GANAPATHY

ART UNIT	PAPER NUMBER
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1623

MAIL DATE	DELIVERY MODE
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07/03/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/540,939	Applicant(s) PERBELLINI ET AL.	
	Examiner Ganapathy Krishnan	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23-43 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 23-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 June 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>7/13/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Specification

The first page of the WIPO document filed 6/23/2005, which has an abstract, has also been used as the abstract sheet in the instant specification. This is not acceptable if the instant claims are determined to be allowable at a later stage. The Office requires the abstract to be typed on a separate sheet of paper even though applicants intend using the abstract on the WIPO document for the instant application. Hence, applicants are requested to kindly type the abstract appearing on the first page of the WIPO document (WO 2004/056877) on a separate sheet and file the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-36, 38 and 39-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29 and 30 recite the term derivatives. It is not clear what all are encompassed by the said term. The specification, at page 2, recites retinoic acids derivatives and refers to a couple of references, both of which mention retinol, retinal and retinamide. It is not clear if applicants intend only these derivatives for those of retinoic acid. There is no definition for the derivatives of butyric acid. In the absence of the specific derivatizations to the chemical core claimed or

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distinct language to describe the structural modifications or the chemical names of derivatives of this invention, the identity of the said derivatives would be difficult to describe and the metes and bounds of said derivatives applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims or clearly defined in the specification.

Claim 36 recites, "at least one of the esters according to claim 35". Claim 35 is drawn to a mixed ester of hyaluronic acid, esterified partly with retinoic acid and partly with butyric acid. It is not clear what applicants intend by the recitation, at least one of the esters according to claim 35.

Claim 38 recites antigenes. Do applicants intend antigens? The claim is examined as drawn to antigens.

Claims that depend from a rejected base claim that is unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

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ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-27, 29, 33 and 35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-5, 12 and 14-15 of U.S. Patent No. 6,897,203 ('203). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Instant claims 23-27 and 35 are drawn to mixed esters of hyaluronic acid, wherein the esterification is partly with retinoic acid and partly with butyric acid and limitations drawn to the degree of substitution and molecular weight. Claims 4-5 and 12 of '203 are also drawn to mixed esters of hyaluronic acid wherein the esterification is partly with retinoic acid and partly with butyric acid.

Instant Claims 29 and 33 are drawn to a process of making the above ester comprising an esterification step of hyaluronic acid with retinoic acid and retinoyl chloride. Claims 14-15 are also drawn to the same process wherein the esterification is done using retinoic acid and retinoyl chloride (retinoyl chloride and retinoic acid in the form of acyl halide are the same).

It would have been obvious to one of ordinary skill in the art at the time the invention was made that instant claims 23-27, 29, 33 and 35 are substantially overlapping with claims 4-5, 12 and 14-15 of the '203 patent. The instant claims must recite limitations that are patentably distinct from those of claims 4-5, 12 and 14-15 of the '203 patent.

Similarity in structure and function and the esterification step using the said acids entails motivation to make the mixed ester and make it via the process step as instantly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23-37 and 39-43 are rejected under 35 U.S.C. 103(a) as being obvious over Rastrelli et al (US 6,897,203).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C.

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102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C.

103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Rastrelli et al teach the preparation of mixed esters of hyaluronic acid, wherein hyaluronic acid is partly esterified with retinoic acid and partly esterified with butyric acid (same as butanoic acid; example 7, col. 9, line 45 through col. 10, line 23). The process involves the use of the ammonium salt of hyaluronic acid, esterification using butyric anhydride (col. 9, line 60-61) and the reactive form of retinoic acid, which is retinoyl chloride (see col. 9, section 7.3 and col. 10, section 7.4, lines 9-10). Rastrelli et al suggest the use of hyaluronan having an average molecular weight ranging from 8000 to 300,000 (col. 2, lines 14-18). Rastrelli et al suggest the activation of the hydroxyl groups as the alcoholate in order to increase the nucleophilicity, before esterification (col. 4, lines 1-3) and also the activation is carried out at a pH ranging from 9 to 11 (col. 4, lines 19-30). The degrees of substitution of hyaluronic acid by butyric acid and by retinoic acid are 0.24 and 0.06 respectively (col.10, lines 20-23). The esters of Rastrelli's

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invention are useful for therapeutic treatment of several conditions and diseases including psoriasis, tumor cell differentiation, treatment of precancerous epithelial lesions and tumors of the breast, cervix, prostate, bladder, colon, oesophagus, larynx, stomach and inflammatory diseases (col. 5, lines 25-62; Example 10 col. 11). Pharmaceutical compositions including different types are also suggested by Rastrelli (col. 6, lines 1-14). However, Rastrelli et al do not teach mixed esters as instantly claimed with a ratio of the degree of substitution with butyric acid and the degree of substitution with retinoic acid of at least 6 and a process wherein the hyaluronic acid is first esterified with retinoic acid before esterification with butyric acid as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the mixed esters of hyaluronic acid, their compositions, make them via the process as instantly claimed and use the said esters in a method of treatment as instantly claimed since analogous mixed esters and their use in methods of treatment are taught in the prior art and are made via an analogous process, the steps of which can be used in a process as instantly claimed.

One of ordinary skill in the art would be motivated to make and use the esters as instantly claimed since the prior art suggests a wide range of degree of substitution and teaches that the esters have minor toxicity and higher stability (col. 5, lines 36-40). One of skill in the art would look for mixed esters of higher stability and reduced toxicity. Obviousness based on similarity of structure and function also entails motivation to make the claimed compounds in expectation that compounds similar in structure will have similar properties. Where prior art compound essentially brackets the claimed compounds and are well known therapeutic agents, one of

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ordinary skill in the art would be motivated to make the claimed compounds in searching for new agents with enhanced therapeutic effects. In re Payne, 606 F. 2d 303, 203, USPQ, 245, 254-55 (C.C.P.A. 1979).

It is well within the purview of one of ordinary skill in the art to reverse process steps. One of skill in the art will recognize from the teaching of the prior art that reversing the esterification step (esterifying first with retinoic acid and then with butyric acid) allows for flexibility in varying the degree of esterification.

Claims 23-37 and 39-43 are rejected under 35 U.S.C. 103(a) as being obvious over Rastrelli et al (US 6,897,203) in view of Perbellini et al (Int. J. Cancer, 1999, 81, 411-416; document # AS in IDS of 7/13/06), Ferrini et al (British Journal of Haematology, 1998, 101(3); Abstract) and Deluca et al (Carcinogenesis, 2000, 21(7), 1271-79.

Rastrelli et al teach the preparation of mixed esters of hyaluronic acid, and their use in methods of treatment of inflammatory diseases and tumors, as explained above. However, Rastrelli et al do not teach mixed esters as instantly claimed with a ratio of the degree of substitution with butyric acid and the degree of substitution with retinoic acid of at least 6 and a process wherein the hyaluronic acid is first esterified with retinoic acid before esterification with butyric acid as instantly claimed.

Perbellini teach the use of butyric acid covalently linked to hyaluronic acid (as the ester) in order to increase the stability and availability of butyric acid. Hyaluronic acid is also known to bind to CD44 receptor expressed on tumor cells (abstract). Hyaluronic acid-butyrate ester was also seen to enhance the inhibitory effect of the drug on breast cancer cell lines compared to that

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of sodium butyrate alone. The degree of substitution of butyrate was found to be around 0.2 for butyrate residue indicated maximum inhibitory effect (page 414, left column, Discussion through page 415 left column lines 1-6). Perbellini teaches the esterification process using butyric anhydride as the esterifying agent (page 412, Figure 1). However, Perbellini does not teach the preparation of the mixed ester or their use in a method of treatment of cellular hyperproliferation as instantly claimed.

Ferrini et al teach the persistence of apoptotic activity of the monosaccharide ester of butyric acid via hydrolysis inside the tumor cells suggests possible use of these for differentiation therapy in AML and HL60 cell lines. However, Ferrini et al do not teach the use of a mixed butyrate and retinoate ester of hyaluronic acid for the same.

DeLuca et al teach the chemoprevention of epithelial carcinogenesis and differentiation therapy using retinoids as the active agents (page 1273).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the mixed esters of hyaluronic acid, their compositions, make them via the process as instantly claimed and use the said esters in a method of treatment as instantly claimed since analogous mixed esters and their use in methods of treatment are taught in the prior art and are made via an analogous process, the steps of which can be used in a process as instantly claimed.

One of ordinary skill in the art would be motivated to make and use the esters as instantly claimed since the prior art suggests a wide range of degree of substitution and teaches that the esters have minor toxicity and higher stability (col. 5, lines 36-40). One of skill in the art would look for mixed esters of higher stability and reduced toxicity. Obviousness based on similarity of structure and function also entails motivation to make the claimed compounds in expectation that

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compounds similar in structure will have similar properties. Where prior art compound essentially brackets the claimed compounds and are well known therapeutic agents, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new agents with enhanced therapeutic effects. In re Payne, 606 F. 2d 303, 203, USPQ, 245, 254-55 (C.C.P.A. 1979).

Claim 38 is rejected under 35 U.S.C. 103(a) as being obvious over Ferrini et al (British Journal of Haematology, 1998, 101(3); Abstract) in view of Vecchio et al (Leukemia 1994, 8, suppl 2; S71 Abstract) and Perbellini et al (Int. J. Cancer, 1999, 81, 411-416; document # AS in IDS of 7/13/06).

Ferrini et al teach the reexpression of CD11a and CD11b on AML and HL60 cell lines using the butyrate esters of monosaccharides. The persistence of apoptotic activity in these esters via hydrolysis inside the tumor cells suggests possible use of these for differentiation therapy. However, Ferrini et al do not teach the use of a mixed butyrate and retinoate ester of hyaluronic acid for the same.

Vecchio et al teach the increased expression of CD11b in APL promyelocytes using all trans retinoic acid (ATRA). However, Vecchio et al do not teach the use of a mixed butyrate and retinoate ester of hyaluronic acid for the same.

Perbellini teach the use of butyric acid covalently linked to hyaluronic acid (as the ester) in order to increase the stability and availability of butyric acid. Hyaluronic acid is also known to bind to CD44 receptor expressed on tumor cells (abstract).

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the mixed butyrate/retinoate esters of hyaluronic acid as instantly claimed and use it in a method for inducing reexpression of CD11a and CD11b on a cell since such a method of reexpression has been taught individually in the prior art using analogous monoester and acid.

One of skill in the art would be motivated to use the mixed esters of hyaluronic acid as instantly claimed since Perbellini teaches that using butyric acid as the ester of hyaluronic acid increase the stability of butyric acid and increase its half life. Since both retinoic and butyric acids are taught to induce reexpression of Cd11 antigens using hyaluronic acid to make the mixed ester is logical as it has several sites for esterification. Hyaluronic acid is also biocompatible (Perbellini Abstract).

Conclusion

Claims 23-43 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK



Shaojia Jiang
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Art Unit 1623